Cleavage of Linear Tetrapeptides into Two Cyclic Dipeptides

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Summary The probability of having *cis*-configuration in the various amide groups of linear tetrapeptides decides whether cyclization or splitting into two cyclic dipeptide molecules is going to occur.

IN spite of the remarkable ease with which certain carboxyl-activated linear tetrapeptides give cyclic tetrapeptides,[1,2] we have now observed that several closely related tetrapeptides do not cyclize under the same conditions, but

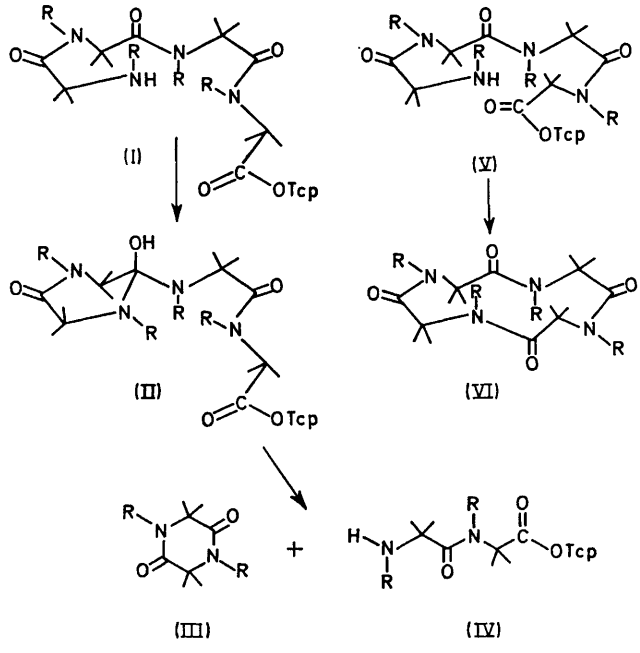
TABLE

Cyclization of tetrapeptides in pyridine at 115°

Linear tetrapeptide (OTcp = 2,4,5-trichlorophenyl)				Cyclic tetrapeptide, yield,		m.p.	Cyclic dipeptides, yields
1	2	3	4				
H-Sar	--- Sar *cis*	--- Sar	--- Sar-OTcp *cis*	c(Sar_4)	43%	>350	
H-Gly	--- Sar *cis*	--- Sar	--- Sar-OTcp *cis*	c($GlySar_3$)	25%	318	
H-Sar	--- Gly *trans*	--- Sar	--- Gly-OTcp *trans*	c(GlySarGlySar)	40%	>350	
H-Sar	--- Gly *trans*	--- Gly	--- Sar-OTcp *cis*	c(Gly_2Sar_2)	10%	310	
H-Sar	--- Sar *cis*	--- Gly	--- Gly-OTcp *trans*	"	traces		c(Sar_2) 25%, c(Gly_2) 10%
H-Gly	--- Sar *cis*	--- Sar	--- Gly-OTcp[a] *trans*	"	none		c(GlySar) 55%
H-L-Ala	--- Sar *cis*	--- Sar	--- Sar-OTcp *cis*	c(L-$AlaSar_3$)	25%	315 subl.	
H-Sar	--- D-Ala *trans*	--- Sar	--- L-Ala-OTcp *trans*	c(D-AlaSar- L-AlaSar)	30%	>350	
H-Sar	--- L-Ala *trans*	--- L-Ala	--- Sar-OTcp *cis*	c(L-Ala_2Sar_2)	10%	290 subl.	
H-Sar	--- Sar *cis*	--- L-Ala	--- L-Ala-OTcp *trans*	"	none		c(Sar_2) 30%, c(L-Ala_2) 13%
H-Aib	--- Sar *cis*	--- Sar	--- Sar-OTcp *cis*	c($AibSar_3$)	none		c(AibSar) 75%, c(Sar_2) 75%

[a] Also cyclized in dimethylformamide–triethylamine at 25° with the same result, but lower yield of cyclic dipeptide.

split up into two molecules of cyclic dipeptides. These tetrapeptides all contain sarcosine combined with either glycine or alanine (in one case with α-methylalanine), and the results when their 2,4,5-trichlorophenyl esters are heated in pyridine are shown in the Table.



A related splitting reaction has been noted for non-activated linear tripeptides, which, however, do not normally cyclize. Thus, Sheehan has found[3] that glycyl-L-histidyl-L-serine gives cyclo(glycyl-L-histidyl) and L-serine, and Meienhofer[4] that D-valyl-L-prolyl-sarcosine splits into cyclo-(D-valyl-L-prolyl) and sarcosine. In both cases cyclization is seen to take place from the amino-end.

The observation that our cyclic dipeptides always correspond to rupture of the central amide bond (Table) shows clearly that the reaction takes place in the linear peptide. A transannular reaction after initial formation of the cyclic tetrapeptide would have permitted the formation also of cyclic dipeptides containing a combination of amino-acid residues 1 and 4 or 2 and 3. One would then also have expected the same cyclic dipeptides in any synthesis leading to a given cyclic tetrapeptide, whereas a widely different product distribution is in fact obtained depending on the choice of tetrapeptide (Table).

Since the *cis*-amide configuration required for cyclic dipeptide formation is obtained much more easily in N-CH_3 amides than in N–H amides,[1,2,5] the two relevant amide bonds in the tetrapeptides have been marked *cis*-allowed and *trans*-preferred, respectively, in the Table. It then becomes apparent that whenever cyclic dipeptides are formed easily, the amide group joining residues 1 and 2 is of the *cis*-allowed type, whereas the amide group joining residues 3 and 4 is generally of the *trans*-preferred type. This can be taken as an argument against a synchronous formation of both rings. Most likely, when the free amino-end of the tetrapeptide (I) cannot reach easily the active ester group, it attacks instead the 2-carbonyl carbon to form an unstable cyclol intermediate (II), which may split up in the alternative direction to give one cyclic (III) and one acyclic (IV) dipeptide. The latter, being an active ester, will subsequently form the second molecule of cyclic dipeptide.

On the other hand, it also becomes apparent that when the yield of cyclic tetrapeptide is particularly high, the same two amide groups, 1–2 and 3–4, of the linear tetrapeptide are either both *cis*-allowed or both *trans*-preferred. This suggests that cyclization takes place whenever the chain has a high probability of being folded in the same way (V) as the

preferred conformation (VI) of the product, which in this type of cyclic tetrapeptides has been shown[1,2,6] to have the sequence *cis,trans,cis,trans*. When the required sequence *cis,trans,cis* or *trans,cis,trans* of the linear tetrapeptide is unlikely, cyclic dipeptide formation takes over, provided the first amide group is *cis*-allowed.

A striking exception is the tetrapeptide containing one residue of α-methylalanine. Cyclization is here prevented, possibly by steric hindrance of the bulky[5] trichlorophenyl ester, or by instability of the product, as a *gem*-dimethyl group can not be accommodated in the strongly favoured cyclotetrapeptide conformation. Product instability is not expected in the nearly flat ring of the cyclic dipeptide. Another interesting observation is that the trichlorophenyl ester of sarcosyl-L-alanyl-sarcosyl-L-alanine upon cyclization gave only a low yield of cyclic products consisting both of the expected LL and the racemized LD isomer; only the latter should be capable of adopting the favoured conformation, which requires opposite configuration at diametric positions. Competition from cyclic dipeptide formation is here unimportant since the first amide group is *trans*-preferred.

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